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Intra-Mesenteric Artery Steroid Administration Relieved Severe Refractory Gastro-Intestinal Graft-Vs.-Host Disease in an Allogeneic Bone Marrow Transplantation Patient

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We report a case of severe gastro-intestinal (G-I) graft-vs.-host disease (GVHD) successfully treated with intra-mesenteric artery steroid administration. A 29-year-old man with severe aplastic anemia (SAA) was submitted to HLA-identical unrelated allogeneic bone marrow transplantation (BMT) and was found to be suffering from grade IV G-I GVHD. Although cyclosporine, steroid pulse therapy, and FK506 proved ineffective, 30 mg of water-soluble prednisolone as administered into each the superior and inferior mesenteric artery with remarkable effects. This treatment was repeated two times, and the symptoms of G-I GVHD disappeared completely. Am. J. Hematol. 56:277–280, 1997.

Key words: intraarterial injection; steroid; therapy; graft vs. host disease; ulcerative colitis

INTRODUCTION

Severe gastro-intestinal (G-I) graft-vs.-host disease (GVHD) often occurs as a result of allogeneic BMT and often causes death. Various treatments have been attempted for severe G-I GVHD, most of them inconsistently have proven effective. G-I GVHD bears a strong resemblance to severe ulcerative colitis in many respects, and the intra-mesenteric artery steroid administration has been very effective for ulcerative colitis. For this reason, we applied the same approach to treat grade IV G-I GVHD and found a striking improvement. We think that our experience with this case carries great therapeutic significance to clinicians striving to control life-threatening severe G-I GVHD.

CASE REPORT

In June 1995, a 29-year-old man was admitted to our hospital to undergo unrelated allogeneic BMT. At 16 years of age, he was diagnosed as having severe aplastic anemia and had been treated with steroid pulse therapy, anti-lymphocyte globulin (ALG), cyclosporine, anabolic steroid hormone, granulocyte colony stimulating factor (G-CSF), and erythropoietin, but all of these treatments were ineffective.

The patient was pretreated with cyclophosphamide (60 mg/kg/day, Day −5, −4, −3, −2) and total body irradiation (total of 8 Gy, Day −1, 0). Then BMT was performed with complete matching of donor (HLA; A31/A24, B39/B52, Cw7/-, ABO; B, Rh+). For prophylaxis of GVHD, short-term methotrexate (MTX) (15 mg/m^2, Day 0, 10 mg/m^2, Day 3, 6, 11), cyclosporine (100–200 mg/day, Day −2~), and ALG (1,000 mg/day, Day −4, −3, −2, −1) were administered. The initial recovery of the patient was satisfactory with no signs of infection. His WBC count was 1,700/mm^3 and his platelet count was 5.3×10^4/mm^3 on the 14th day after transplantation. Engraftment of the transplanted bone marrow was thus confirmed. However, watery diarrhea (5 times/day; total

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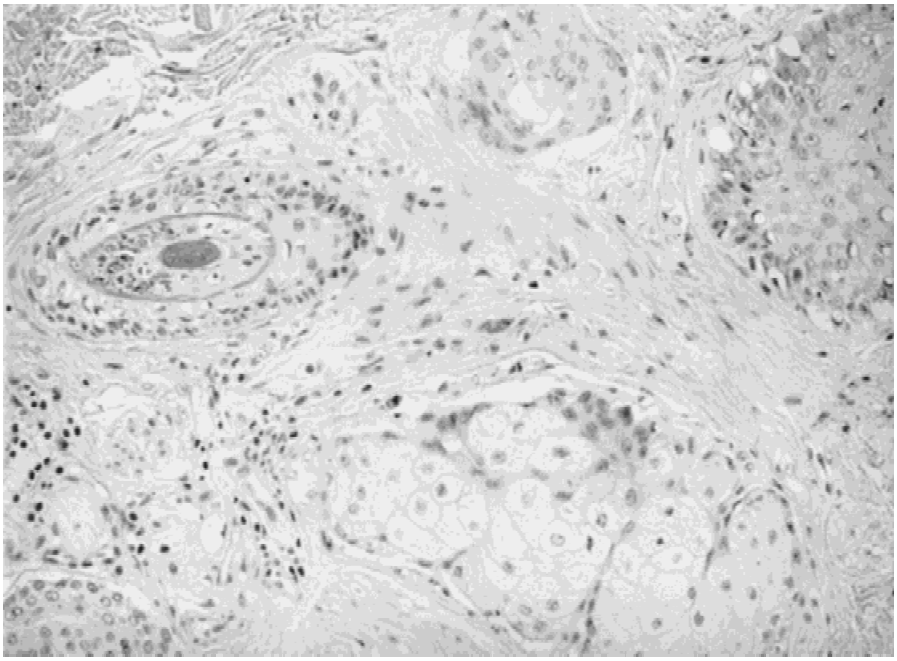

Fig. 1. Skin biopsy on 30th post-transplantation day revealed diffuse lymphocytic infiltrates in the upper dermis and basal cell vacuolization.

volume: 650 ml/day) developed from the 27th post-transplantation day. Erythema manifested on over 50% of the body, and liver dysfunction was indicated by a total bilirubin level of 2.1 mg/dl. Skin biopsy on the 30th post-transplantation day revealed diffuse lymphocytic infiltrates in the upper dermis and basal cell vacuolization (Fig. 1). Although lower G-I tract biopsy was not done, enterocolitis induced by cytomegalovirus (CMV) was excluded by the polymerase chain reaction (PCR) method. Several stool cultures yielded no enteric pathogens. Antibody titers against viruses other than CMV were within normal range. Thus acute GVHD (Grade IV) was diagnosed. After steroid pulse therapy was conducted four times and cyclosporine was replaced with FK506, the dermatological symptoms and hepatic dysfunction showed tendencies to improve. However, the G-I tract symptoms became markedly worse: the frequency of bowel movement and volume (2,000 ml/day) of stool increased, stool became bloody and the patient experienced severe abdominal pain and paralytic ileus. The patient's symptoms became so severe that it was feared his life was at risk. Then we administered 30 mg of water-soluble prednisolone into each the superior and inferior mesenteric artery on both the 40th and 44th post-transplantation days. Within about 6 h after the first intra-arterial administration, there was a striking decrease of stool volume, though blood was still present. The symptoms of G-I GVHD disappeared completely after the second administration of prednisolone, and the character of the stool became normal (Fig. 2).

The subsequent course of the patient's health showed marked improvement, but sudden death occurred due to a cerebral hemorrhage on the 50th post-transplantation day. Autopsy revealed mild desquamation of the mucosa of the large intestine, but there was no evidence of fresh intestinal bleeding. With the microscopic view, there was no lymphocyte infiltration (Fig. 3). As a result, it was surmised that the intra-arterial administration of prednisolone had been very effective in the treatment of the G-I GVHD in this patient.

DISCUSSION

G-I GVHD arising from allogeneic BMT and escalating to grade IV often causes death by inducing severe systemic infection or hepatic veno-occlusive disease [1–5]. Various treatments have been attempted for severe G-I GVHD, including steroid pulse therapy, administration of MTX, cyclosporine, FK506, etc. However, most of them have proven unreliable [6,7]. In our case, acute GVHD occurred in spite of prophyraxic administration of cyclosporine and FK506.

It has been pointed out that an imbalanced production of cytokines is involved in the development of severe G-I GVHD [8–10] similar to ulcerative colitis, and the symptoms in patients with G-I GVHD bear a strong resemblance to those of severe ulcerative colitis patients to whom steroids were administered intra-mesenteric arterially with remarkable effects [11]. For this reason, we applied the same approach to treat severe G-I GVHD after unrelated allogeneic BMT, administering 30 mg of

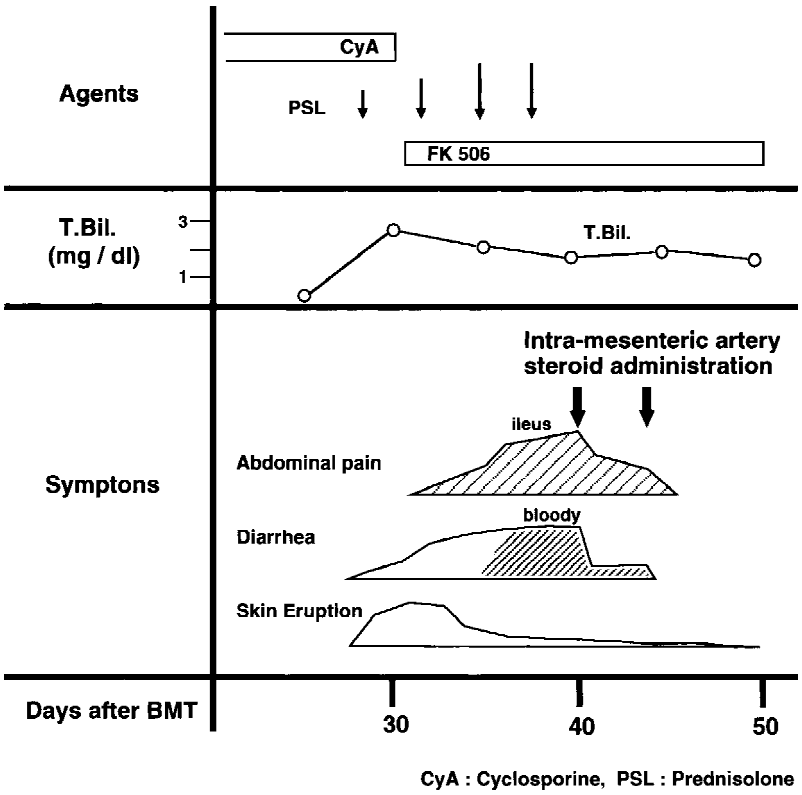

Fig. 2. Clinical course of this patient. The symptoms of severe G-I GVHD disappeared after intra-mesenteric artery steroid administration.

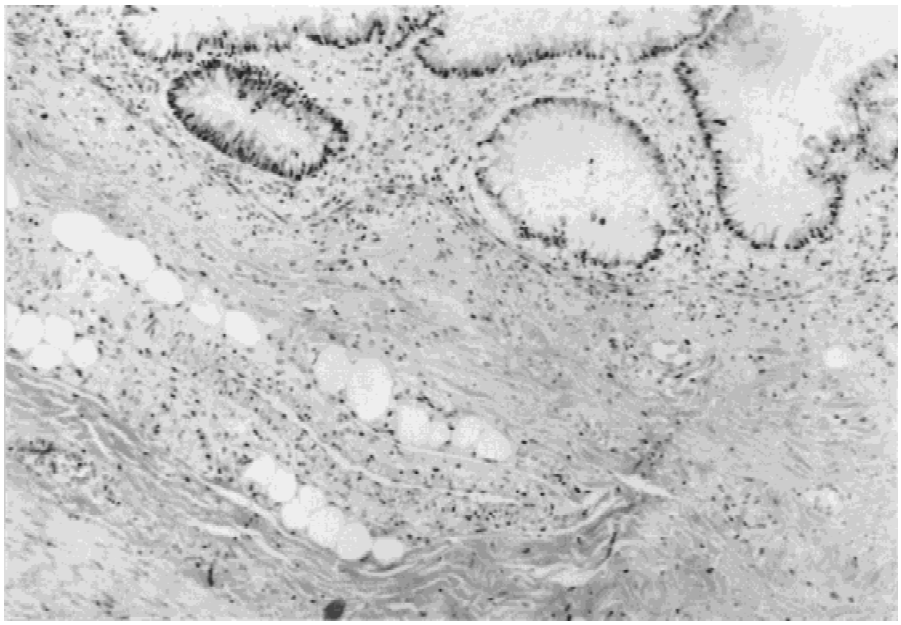

Fig. 3. Microscopic views reveal mild desquamation of large intestinal mucosa, but no lymphocyte infiltration or fresh bleeding is observed (H-E stain, ×250). Pathologically, it is surmised that the intra-mesenteric artery steroid administration was very effective for the treatment of severe G-I GVHD.

water-soluble prednisolone into each the superior and inferior mesenteric artery and found a striking improvement.

A review of the published literature did not reveal any previous reports of intra-arterial steroid administration for the treatment of G-I GVHD. We have applied this treatment to only the one case reported here, but its efficacy was very dramatic. We concluded that our experience with this case warranted reporting because it carries great therapeutic significance to clinicians striving to control life-threatening severe G-I GVHD.

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